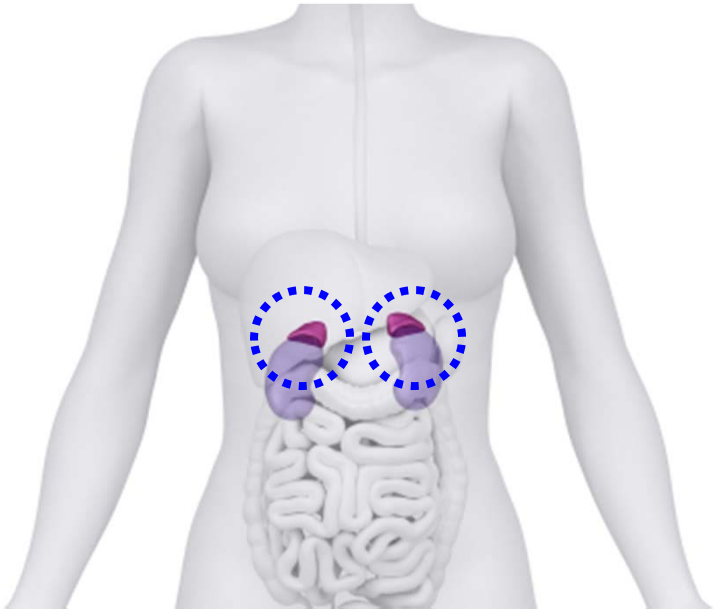
Congenital Adrenal Hyperplasia in Women

From the Fetus to Adulthood



Case: A lean 22 y/o woman is hirsute and has oligomenorrhea. She presents because of infertility (the absence of pregnancy after 1 year of regular, unprotected sex). ***What is in the differential diagnosis of infertility in a hirsute woman?***

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Learning objectives

At the conclusion of this presentation, the laboratorian will be able to:

- List a differential diagnosis of hirsutism and infertility

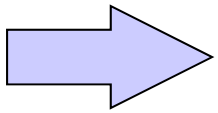
- Classify and differentiate the different varieties of CAH

- Diagnose and treat late-onset CAH

Differential diagnosis of infertility in a hirsute woman:

Polycystic ovarian syndrome (PCOS; associated w/ MS)

Medications (e.g., danazol for endometriosis)

Late-onset congenital adrenal hyperplasia 

Cushing syndrome

Androgen secreting tumors (ovarian or adrenal)

Precocious adrenarchy (early-onset axillary and/or pubic hair)

What is congenital adrenal hyperplasia (CAH)?

(I) Inborn error in steroid biosynthesis: variable impairment in the synthesis of:

~ Cortisol (alone)

(or)

Cortisol & Aldosterone

(II) Disordered adrenal androgen production

- Shared biosynthetic pathways w/ testes & ovary

- **Adrenal androgens:** **precursors of estrogens**
  precursors of androgens

What are the consequences of disordered *adrenal androgen* synthesis in congenital adrenal hyperplasia (CAH)?

Excess	Males	Females
In utero	Genital hyperpigmentation	Virilization -- > 46,XX DSD
Ex utero	Precocious puberty	Accelerated growth (children); virilization

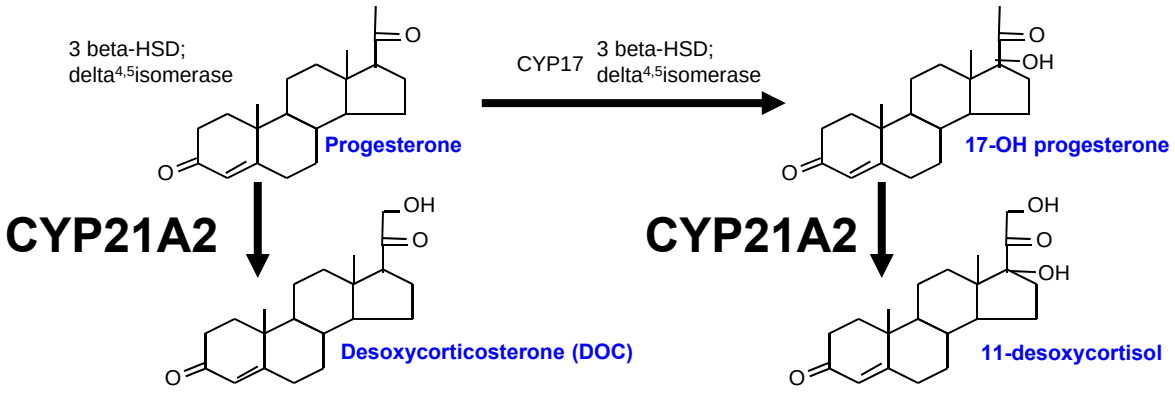
Testosterone deficiency	Males	Females
In utero	Inadequate virilization 46,XY DSD v	No adverse effect
Ex utero	46,XY DSD	No adverse effect

What is the most common form of congenital adrenal hyperplasia (CAH)?

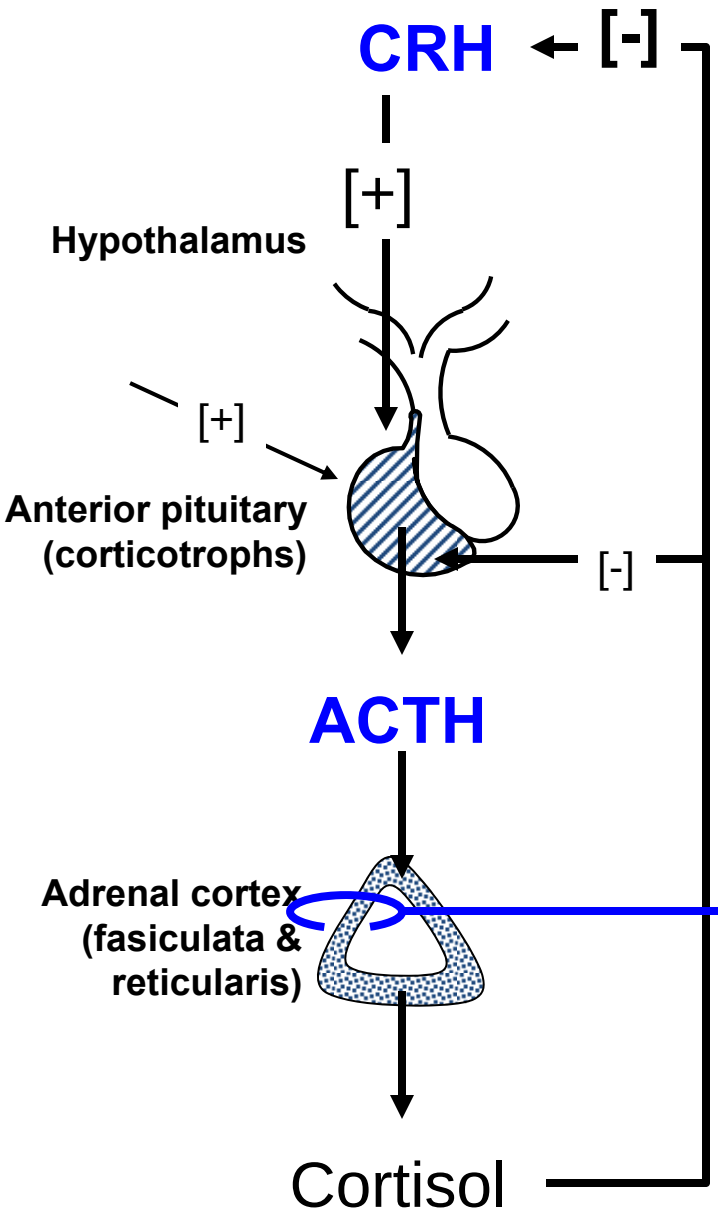
Def. of 21-alpha hydroxylase (21-OHylase)

- Formal gene name: CYP21A2*

*Cytochrome P450, Family 21, Subfamily A, Polypeptide 2
CYP21A1P = Cytochrome P450, Family 21, Subfamily A, Polypeptide 1 Pseudogene



What regulates the expression of 21-OHylase?



Enzymes regulated by ACTH

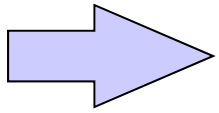
StAR	
20,22 desmolase*	(CYP11A)[1]
17-OHylase	(CYP17)[1]
3-beta HSD	
21-OHylase	(CYP21A2)
11-beta hydroxylase	(CYP11B1)

StAR = steroid acute regulatory protein; transports chol into adrenal cortical cells; * a.k.a. – side-chain cleavage enzyme.
(1) Excellent data for their regulation by ACTH

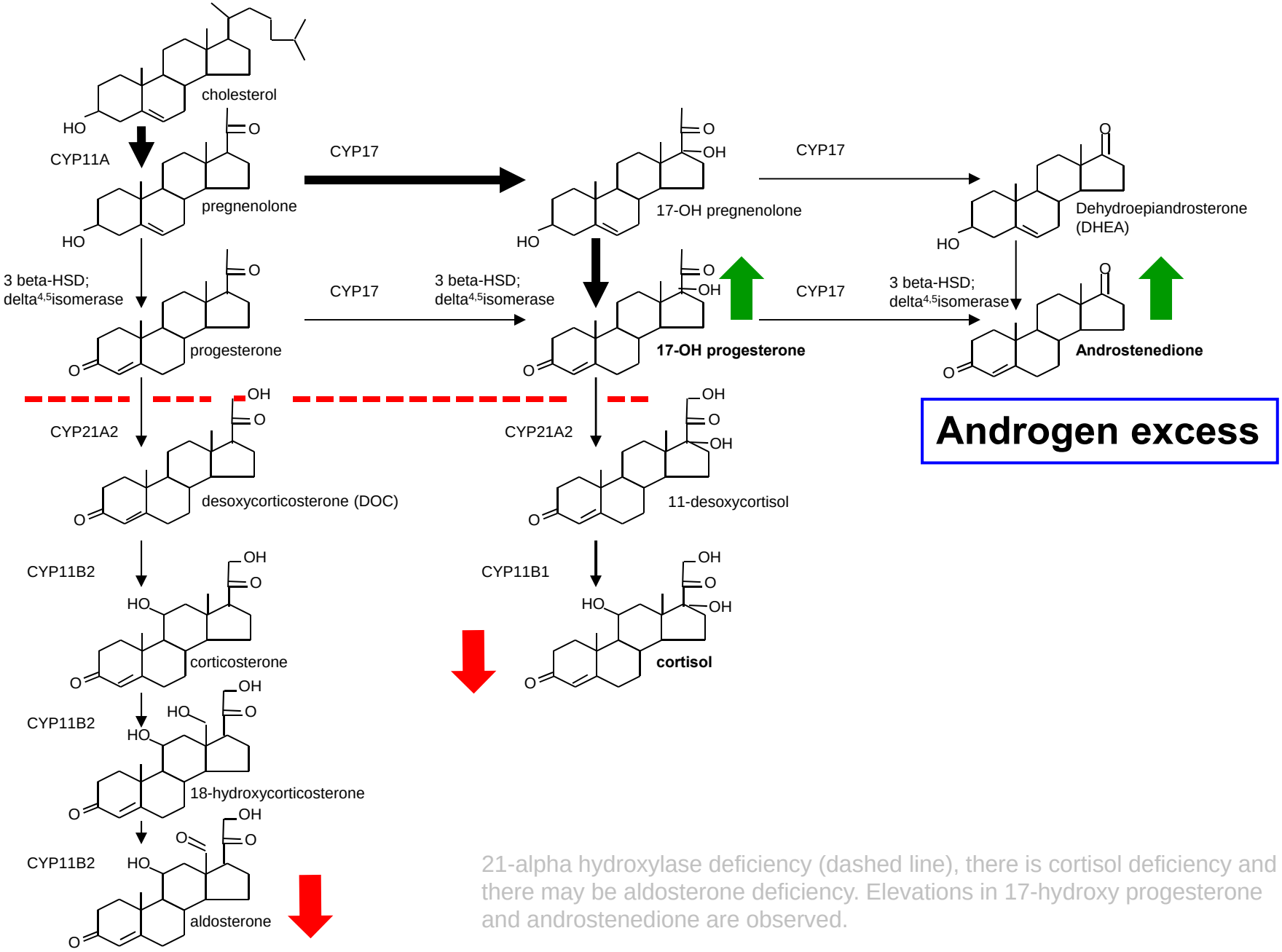
What are the consequences of adrenal steroid hormone deficiency?

Hormone def.	Consequences:
Cortisol	Lack energy, N/V, weight loss, hypoglycemia, hyponatremia, vascular collapse, hypotension, shock, death
Aldosterone	Hyponatremia, hyperkalemia, acidosis, hypovolemia, hypotension, shock, death

What is the biochemistry of 21-OHylase def.?



21-alpha hydroxylase deficiency



21-alpha hydroxylase deficiency (dashed line), there is cortisol deficiency and there may be aldosterone deficiency. Elevations in 17-hydroxy progesterone and androstenedione are observed.

What are other forms of CAH?

Other types of CAH:

11-beta hydroxylase def.

17-alpha hydroxylase def.

3-beta hydroxy steroid dehydrogenase def. (3-beta HSD def.)

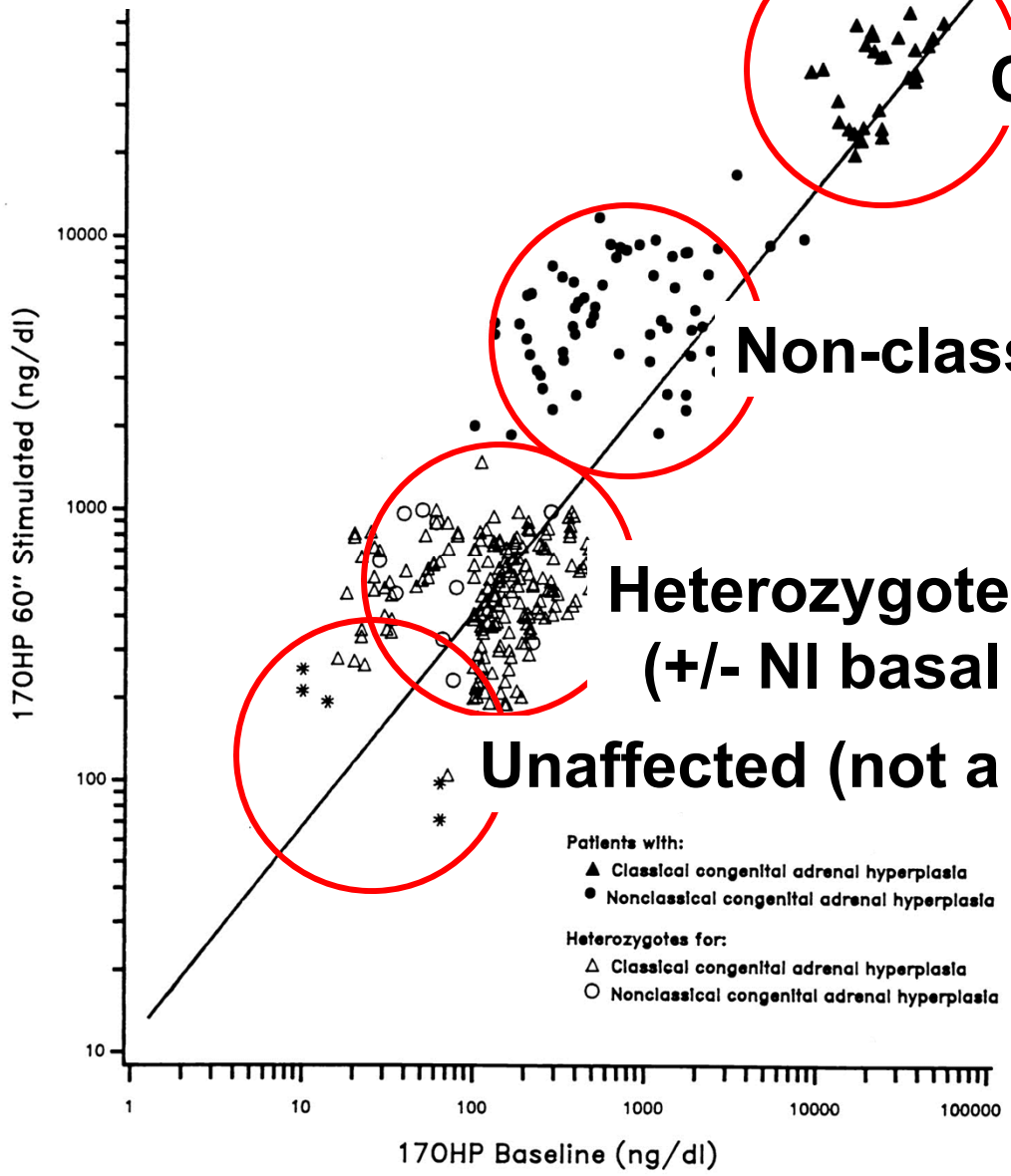
Lipoid CAH [steroidogenic acute regulatory (StAR) protein def.]

What is the range of consequences of 21-OHylase def.?

Severity	Classification	Phenotype of 21-OHylase CAH	Age of onset
++++	Classical	Salt-wasting	Newborns
+++	Classical	Simple virilizing	Newborns
++	Nonclassical*	Late-onset	Late childhood, adolescence or adulthood
+	Heterozygous carrier	Asymptomatic	N/A

*Attenuated; N/A = not applicable

Relationship of basal & ACTH-stimulated 17-OHP to 21-OHylase CAH phenotype



60 min 17-OHP post-ACTH

Classical CAH

Non-classical CAH

Heterozygotes
(+/- NI basal 17-OHP)

Unaffected (not a carrier)

17-OHP baseline

What is effect of *salt-wasting* or *simple virilizing* CAH on the development of the external genitalia in the 46,XX fetus?

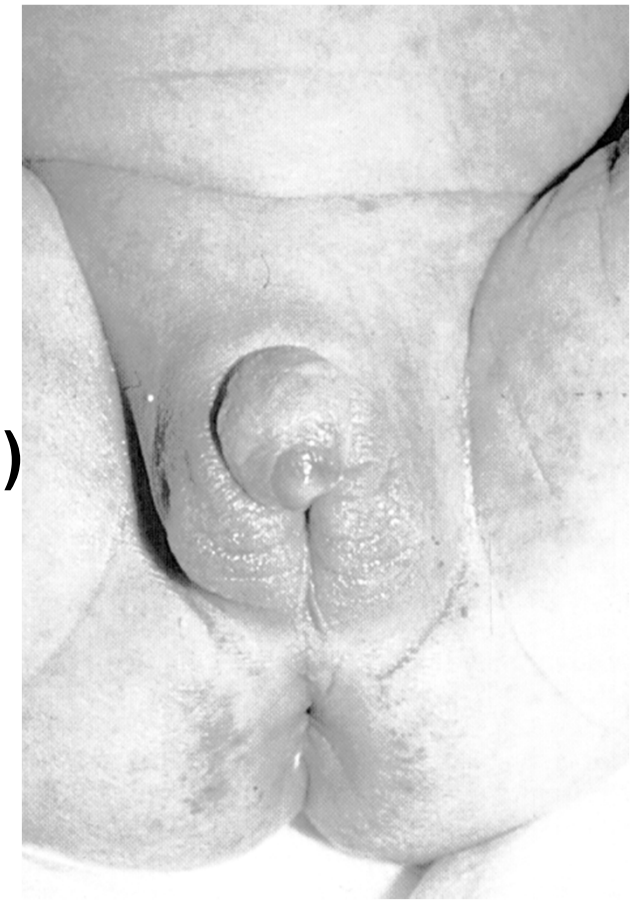
Excess adrenal androgens (androstenedione & DHEA)

v

Virilization of external genital

V

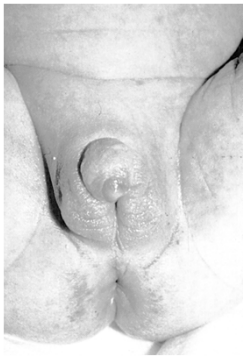
Disorder of sexual development (DSD) [46,XX, DSD]



How do salt-wasting and simple virilizing CAH differ?

More severe

	DSD	Cortisol def.	Aldo-sterone def.	Addisonian crisis (if untx'ed)
Salt -wasting	Yes	Yes	Yes →	Yes
Simple virilizing	Yes	Yes	No →	No



What is the epidemiology of late-onset of 21-OHylase def.?

Hz: 1 in 1000

Incr. Hz in: Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations

Note: Dx may be missed in boys

What is the *phenotype* of late-onset of 21-OHylase def. in females?

Androgen excess:

Hirsutism (59%), acne (33%), androgenic alopecia, anovulation, menstrual dysfunction (54%: oligomenorrhea) & infertility

Prepubertal:

+/- Tall stature, advanced skeletal maturation, and premature development of pubic hair, axillary hair, and adult apocrine odor; +/- clitoromegaly

Women: Polycystic ovary-like phenotype

Note: Boys may have penile enlargement with prepubertal testes.

How is the diagnosis of late-onset CAH established?

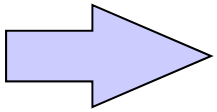
Compatible clinical history of androgen excess:

Girls: +/- premature adrenarchy, accelerated growth

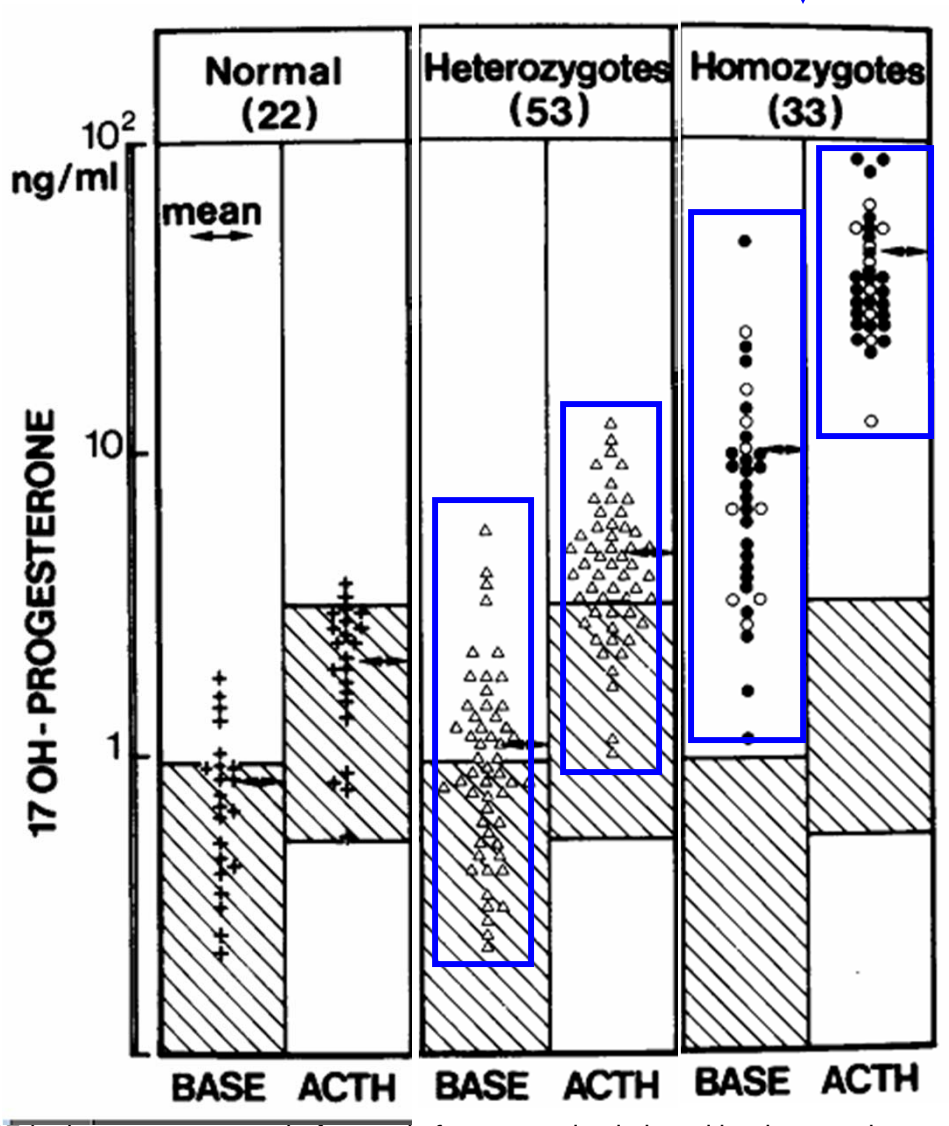
Girls, adolescents/women: acne, hirsutism

Adolescents/women: menstrual dysfunction & infertility

Elevated basal and 60 min. post-ACTH 17-OHP



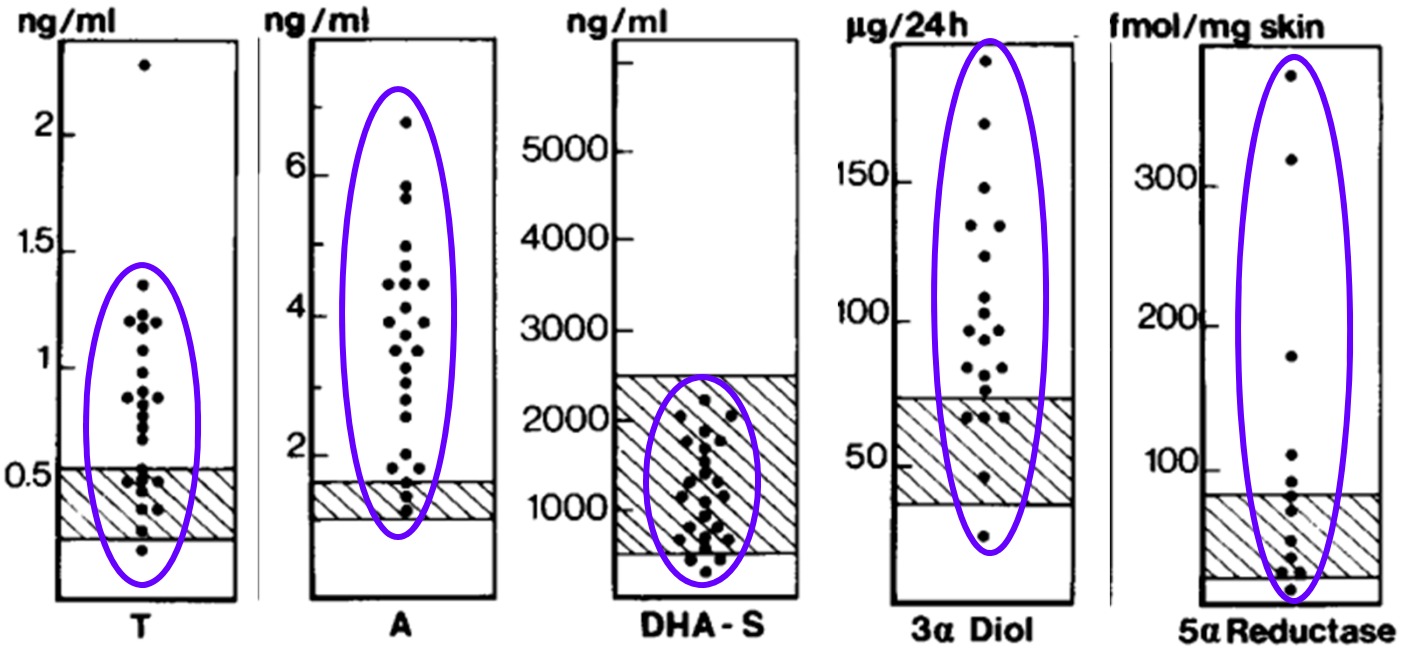
17-OHP concentrations in late-onset CAH



Normal range

Plasma concentrations of 17-hydroxyprogesterone before and after acute stimulation with adrenocorticotropic hormone (ACTH) in patients with late-onset 21-hydroxylase deficiency and members of their families. Closed circle, proband; open circle, homozygotes; open triangle, heterozygotes; plus sign, normals.(Kuttenn F, Couillin P, Girard F et al: Late-onset adrenal hyperplasia and hirsutism. N Engl J Med 313:2224, 1985.)

Other hormone measurements in late-onset CAH



T = **Testosterone**

A = **Androstenedione**

DHA-S = **Dehydroepiandrosterone sulfate**

3α Diol = **Urinary 3α-androstanediol glucuronide***

5α reductase = Activity of T -- > DHT converting enzyme

Figure 1. Androgen Levels in 24 Women with Late-Onset Adrenal Hyperplasia.
T denotes plasma testosterone, A androstenedione, DHA-S dehydroepiandrosterone sulfate, 3α Diol urinary 3α-androstanediol glucuronide, and 5α Reductase skin capacity for 5α-reduction of testosterone. Hatched areas indicate normal ranges.
To convert values for testosterone and androstenedione to nanomoles per liter, multiply by 3.467; to convert values for dehydroepiandrosterone, multiply by 2.620; to convert values for androstanediol, multiply by 3.424.

*** Marker of peripheral androgen metabolism**

What are *complications* of late-onset of 21-OHylase def.?

Adrenal tumors

Adrenal hypertrophy

Adrenal myolipoma (rare)

What is in the *differential diagnosis* of late-onset of 21-OHylase def.?

Conditions producing hirsutism and/or menstrual irregularities (including infertility)

Polycystic ovarian syndrome (PCOS)

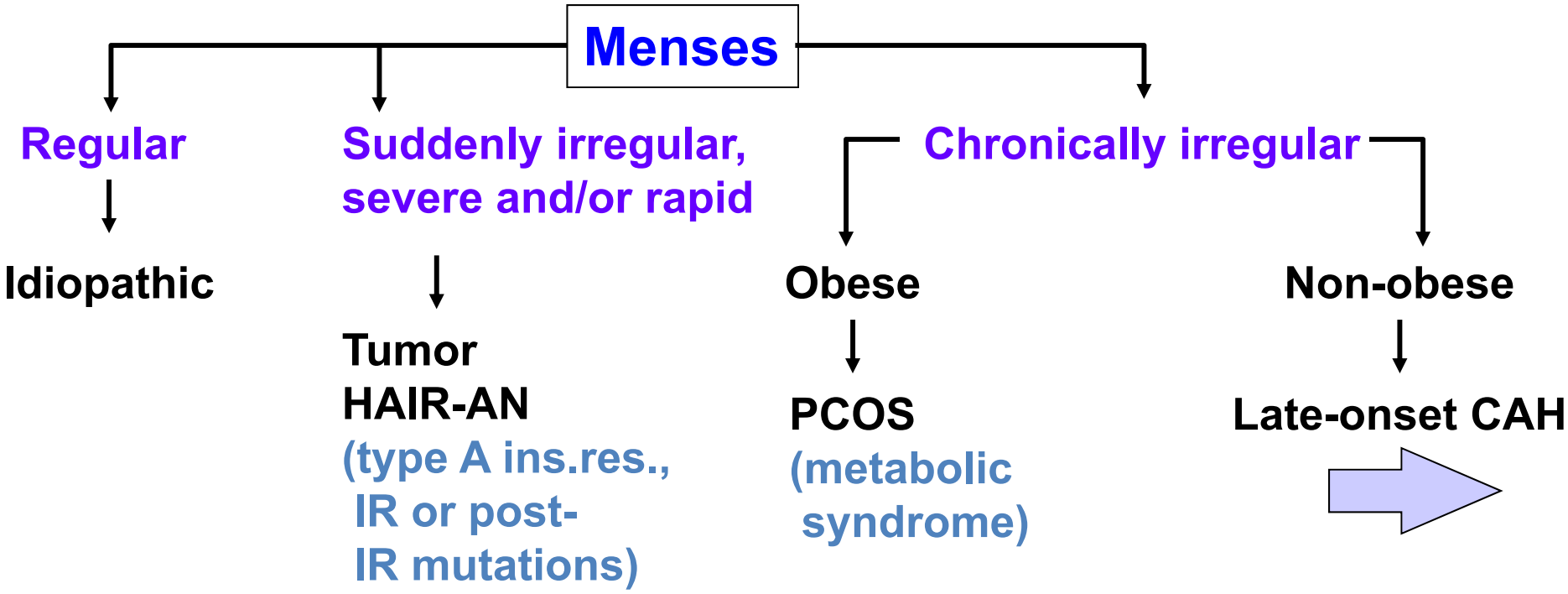
Medications (e.g., danazol for endometriosis)

Cushing syndrome

Androgen secreting tumors (ovarian or adrenal)

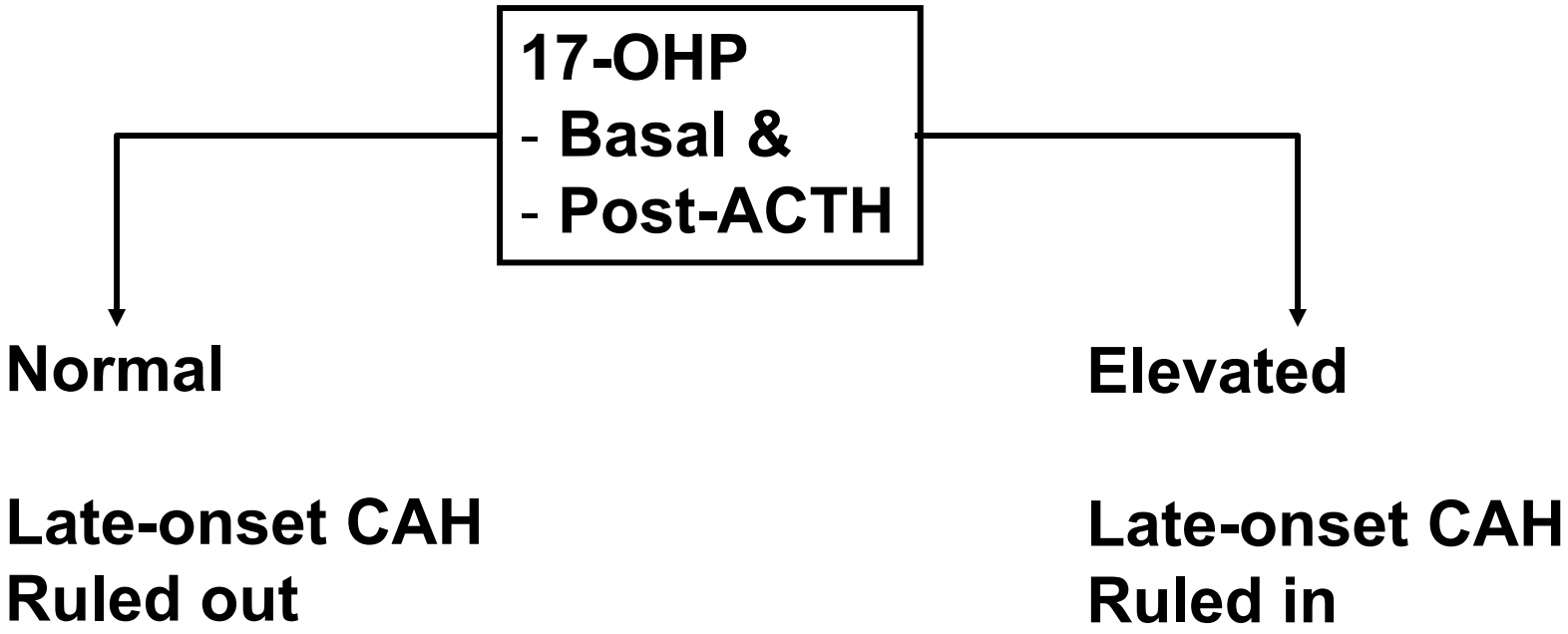
Precocious adrenarchy (early-onset axillary and/or pubic hair)

How can hirsutism be evaluated (not exhaustive)?



HAIR-AN syndrome is defined as a constellation of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).

How is late-onset of 21-OHylase def. excluded from the differential diagnosis of hirsutism or menstrual irregularity (including infertility)?



How and when should late-onset of 21-OHylase def. be treated? (1)

Girls & boys	Treatment	Goal
W/ pre-, early puberty (+) incr. BA	Glucocorticoids (+/- GnRH agonist for precocious puberty)	Decr. rate of skeletal maturation incr. final height
Pubertal girls		
ACTH-stimulated Cortisol: <18 mcg/dL	Glucocorticoids	Tx glucocorticoid def.; prevent Addisonian crisis
=> 18 mcg/dL	Glucocorticoids	Tx at times of stress; prevent Add.crisis

BA = bone age

How should late-onset of 21-OHylase def. be treated in adult women? (2)

	Comments
Oral contraceptives	+/- decr. ovarian androgen secretion, improve acne, slow hirsutism, restore menstrual cyclicity
Antiandrogens*	+/- helpful for hirsutism androgenic alopecia

* spironolactone, flutamide, cyproterone acetate, or finasteride

SUMMARY

Classical 21-OHylase CAH

Fetus -- > virilization: 46, XX DSD

Newborn: +/- Addisonian crisis
- salt-losing *versus* simple virilizing

Late-onset CAH (nonclassical CAH): common disorder

Presents as hirsutism, menstrual irregularity, infertility

Men: ~asymptomatic

Tx. w/ glucocorticoids if low cortisol response to ACTH

THE END